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Please find below and/or attached an Office communication concerning this application or proceeding.

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/770,562
Filing Date: January 26, 2001
Appellant(s): CURATOLO ET AL.

Dennis E. Stenzel
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 12/18/09 appealing from the Office action mailed 11/09/09.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

0 344 603	MIYAJIMA et al	12-1989
0 784 974 A1	KIGOSHI et al	7-1997

57-176907	HIKOSAKA et al	10-1982
6,147,072	BYMASTER et al	11-2000

Madhusoodanan S. et al. "Efficacy of risperidone treatment for psychoses associated with schizophrenia, schizoaffective disorder, bipolar disorder, or senile dementia in 11 geriatric patients: a case series" Journal of Clinical APsychiatry, Vol 56 (Nov 1995), Abstract.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 4, 49-51 and 53-56 are rejected under 35 U.S.C. 102(b) as being anticipated by Miyajima et al. (EP 0 344 603).

Miyajima describes a composition comprising NZ-105 and HPMCAS (page 3, lines 16 and 17). Miyajima describes preparing the composition by dissolving NZ-105 and HPMCAS in an organic solvent and removing the solvent by vacuum drying, spray drying or freeze drying to yield compositions that have remarkably enhanced bioavailability (page 3, lines 16-20; page 4, lines 56-58) with solid dispersions resulting from spray-drying. NZ-105, is a dihydropyridine

phosphonic acid derivative drug that is poorly soluble in water (abstract; page 2, lines 14-35; page 3, lines 6-9). 1-7 parts or 3-5 parts by weight of HPMCAS are used per 1 part by weight of NZ-105 (page 5, lines 8 and 9) so that the ratio of the drug to polymer in Miyajima is 1:1 to 1:7 or 1:3 to 1:5 are species of the broader ratio of 1:0.4 to 1:20 and the narrower range or species anticipates the broader range meeting the drug polymer ratio of claims 1, 55 and 56. Claim 51 is a product by process claim and the claim is thus met by the composition of Miyajima. For claim 1, parts (a) and (b) are the properties of the dosage form. Claim 1 recites spray dried dispersion which in claim 4 is amorphous when undispersed and the recitation in claim 4 is also directed to the properties of the dosage form. "Spray dried" is the process of making the dispersion, however, the product in Miyajima is also spray dried. Claims 4, 49, 53 and 54 recite the properties of the composition so that the composition of Miyajima meets the claims. The solvent is removed by vacuum drying, spray-drying or freeze-drying and the dried product is inherently free of solvent and Miyajima did not say that the product has associated solvent so that claim 50 is met. The particle size of 100-400 or 150-300 mesh of the Miyajima particles encompasses the particles size of 100 micron since 400 and 300 mesh sizes are less than 100 micron.

Claims 1, 4, 49-51 and 53-56 are rejected under 35 U.S.C. 102(a) as being anticipated by Kigoshi et al. (EP 0 784 974).

Kigoshi describes solid dispersions containing xanthine derivatives and polymer (title; abstract; page 2, lines 21, 22, 44, 45); the xanthine derivatives are slightly soluble in water (page 2, lines 21 and 22) meeting the sparingly water soluble drug of the claims; the polymer can be a

cellulose derivative (page 3, line 58) with enteric coating polymers preferred (page 4, line 5) and hydroxypropylmethyl cellulose acetate succinate (HPMCAS) is one the preferred derivatives named (page 4, line 8) meeting the requirements of claim 1. One of the processes of removing the solvent from the formation of the solid dispersion is by spray-dry granulator (page 4, line 38) and the resulting granules/particles are isolated (page 4, lines 49, 50). The ratio of the xanthine derivatives of compound I to the polymer ranges from 3:1 to 1:5 (page 4, lines 12, 13) with the ratio of 1:5 intersecting points within the recited ratio of from 1:0.4 to 1:20 of the claims; also a ratio of 1:1 is preferred (page 4, line 15); so that disclosed ratio meets the requirements of claims 1, 55 and 56. Claim 1 recites spray dried dispersion which in claim 4 is amorphous when undispersed and the recitation in claim 4 is also directed to the properties of the dosage form. Claims 4, 49, 53 and 54 recite the properties of the composition so that the composition of Kigoshi meets the claims. Claim 51 is a product by process claim and the claim is thus met by the composition of Kigoshi. Claim 1 recites spray dried dispersion which in claim 4 is amorphous when undispersed and the recitation in claim 4 is also directed to the properties of the dosage form. "Spray dried" is the process of making the dispersion, however, the product in Kigoshi is also spray dried. The solvent is removed by vacuum drying, spray-drying or freeze-drying and the dried product is inherently free of solvent and Kigoshi did not say that the product has associated solvent so that claim 50 is met.

Claims 1, 4, 49, 53, 54, 55 and 56 are rejected under 35 U.S.C. 102(b) as being anticipated by JP 57-176907 (Eng. Translation provided by applicant in 1449 filed 5/07/2001).

JP 57-176907 discloses composition comprising AS-56C in substantially amorphous form in one or more bases selected from hydroxypropyl methyl cellulose phthalate, HPMCAS, methyl acrylate-methacrylic acid-methacrylate copolymers and methacrylic acid-methyl methacrylate copolymers (first full paragraph of page 2); the product is obtained by spray drying (4^{th} full paragraph page 2); the ratio of drug AS-56C to polymer ranges from 1:4, 1:3, 1:2, 1:20 in Examples 1-12. The ratios meet the ratio requirements for the drug to polymer of claims 1, 55 and 56. Claims 4, 49, 53 and 54 recite the properties of the composition so that these claims are met. Since the composition of JP 57-176907 spray dried just as the claimed composition, the composition of the JP 57-176907 is a dispersion and the drug is molecularly dispersed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 23, 50 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyajima et al. (EP 0 344 603) or Kigoshi et al. (EP 0 784 974).

Miyajima: Miyajima is described above as anticipating claim 1. For claims 50 and 51, since the formulation of Miyajima and that of the instant claims are spray dried, it would be reasonable to expect that the residual solvent in the formulation of Miyajima and the composition of the claims would be the same except where applicant shows that's not to be the case. Although, Miyajima's spray dried formulations are granules, Miyajima does not specifically teach the particle size is less than 100 μm in diameter. But, the particle size of 100-400 or 150-300 mesh of the Miyajima particles encompasses the particles size of 100 micron since 400 and 300 mesh size are less than 100 micron. Therefore, the particles of Miyajima at 400 or 300 mesh (37 μm and 53-44 μm) are less than 100 micron. Therefore, taking the teachings of Miyajima, one having ordinary skill in the art at the time the invention was made, would reasonably expect that the particles of the dispersion would have sizes that are less than 100 μm according to the disclosed size of 100-400 and 150-300 mesh (149-37 μm and about 105-44 μm) according to the disclosure of Miyajima.

Kigoshi: Kigoshi has been described above as anticipating claim 1. For claims 50 and 51, since the formulation of Kigoshi and that of the instant claims are spray dried, it would be reasonable to expect that the residual solvent in the formulation of Kigoshi and the composition of the claims would be the same except there is factual evidence that it's not. Although, Kigoshi's spray dried formulations are granules, Kigoshi does not specifically teach the particle size of claim 23. But, in example 1, the particle size is 200 mesh (74 μm) and since other

polymers such as the HPMCAS are contemplated (see claims 5 and 6), it is reasonable to expect that when the other polymers such as hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, or carboxymethylethyl cellulose (see claims 5 and 6) are used, the drug and polymer solution when also be sprayed onto a seed of 200 mesh (74 μm) would form dispersed solids having size of 200 mesh (74 μm) which is less that 100 micron. Therefore, taking the teachings of Kigoshi, one having ordinary skill in the art at the time the invention was made would reasonably expect that solution of drug and HPMCAS when sprayed onto a core particle having the size of 200 mesh (74 μm) would expectedly result in dispersion of drug and HPMCAS having a size of 74 μm, which is less than 100 μm.

Claims 1, 4, 36, 37 49-51 and 53-56 rejected under 35 U.S.C. 103(a) as being unpatentable over Kigoshi et al. (EP 0 784 974) in view of Madhusoodanan et al. ("Efficacy of risperidone treatment for psychoses associated with schizophrenia, schizoaffective disorder, bipolar disorder, or senile dementia in 11 geriatric patients: a case series," in J. Clin. Psychiatry, 1995 Nov;56(11):514-8 (Abstract enclosed)) and further in view of Bymaster et al. (US 6,147,072).

Kigoshi has been described as teaching the limitations of claim 1 and dependent claims 4, 49-51 and 53-56. The active agents in Kigoshi are xanthine derivatives and these derivatives have anti-dementia activity in addition to diuretic activity, kidney protecting activity and cerebral function-improving activity (page 2, lines 5-8).

The xanthine derivatives are not the antipsychotic drugs of claims 36 and 37. But, drugs such as the antipsychotic drug, risperidone is known in the art to have effect on psychosis related

to dementia, bipolar disorder and schizophrenia according to the abstract of Madhusoodanan in J. Clin. Psychiatry, 1995 Nov. Further also, risperidone and ziprasidone are known anti-psychotic drugs (see Bymaster at column 2, lines 22 and 43). One anti-dementia agent can be used in place of the other with the expectation that either will deliver the desired anti-dementia effect.

Therefore, taking the teachings of Kigoshi, Madhusoodanan and Bymaster, one having ordinary skill in the art at the time the invention was made would reasonably expect that solid dispersions obtained by substituting ziprasidone for the xanthine derivatives in Kigoshi would have the expected anti-dementia activity in a person in need thereof.

(10) Response to Argument

Claims 1, 4, 49-51 and 53-56 are anticipated under 35 U.S.C. 102(b) by Miyajima et al. (EP 0 344 603) or Kigoshi et al. (EP 0 784 974).

Response: Appellant's arguments filed 11/23/09 have been fully considered but they are not persuasive.

Miyajima: Appellant argues that Miyajima does not teach how to make NZ-105 composition by spray drying because a) Examples 1-5 show the preparation of "four-component" by spraying the solution containing NZ-105 onto a fourth component using a fluidized bed granulation apparatus and b) Example 6 shows how to prepare "three-component composition" by drying the mixture in vacuo and as such, the Miyajima methods do not use spray drying and spray drying method is not enabled by Miyajima.

The examiner disagrees with appellant that Miyajima does not teach spray drying as one of the processes for preparing the formulation of NZ-105 and HPMCAS in view of the following:

i) Miyajima positively contemplates removing the solvent by vacuum drying or spray drying or freeze drying (see page 5, line 57) and a reference is not limited to its working examples and evaluation of Miyajima shows that the public is apprised that spray drying can be used to remove the solvent. ii) Since Miyajima is not limited by the examples, and since there is a positive disclosure in Miyajima that solvent can be removed by spray drying, it is thus clear that spray drying a formulation comprising NZ-105 and HPMCAS is anticipated. iii) The comprising language of appealed claim 1 is open and the "four-component" or "three-component" compositions of Miyajima is not excluded from the composition of appealed claim 1. iv) The technique of spray drying is very well known in the pharmaceutical formulation art as a means of removing solvent to effect drying of compositions. v) Furthermore, the decision in *in re Gay*, 135 USPQ 311 (C.C.P.A. 1962) established that there is no specific requirement for the disclosure of a specific example, that a patent specification is neither intended nor required to be a production specification, and that the absence of a specific example is not necessarily evidence that the best mode has not been disclosed (see also MPEP 2165.01 [R-2] II). Therefore, appellant's argument that Miyajima does not enable spray drying is not persuasive.

Kigoshi: Appellant admits that Kigoshi product is a solid amorphous dispersion. While appellant appears to concede that solid dispersions comprising HPMCAS and xanthine derivatives can be made from the broad teachings of Kigoshi according to the full paragraph bridging pages 4 and 5 of the appeal brief filed 11/19/09, appellant is convinced, on page 5, first

full paragraph, that Kigoshi does not teach how to prepare two component dispersion of drug and HPMCAS or any dispersion by spray drying because Examples 1-3 of Kigoshi show how to make three-component dispersions of drug, methacrylate copolymer and lactose by fluid bed granulation and Examples 4 and 5 show how to prepare dispersions of drug and methacrylate copolymer by heat-melt-kneading using an extruder.

The examiner disagrees with appellant that Kigoshi does not disclose solid dispersions of drug and HPMCAS in view of the following:

vi) Kigoshi discloses solid amorphous dispersions as admitted by appellant. The appealed claims are directed to compositions and not to the method of making the compositions. vii) The comprising language of appealed claim 1 is open and the "three-component" compositions of Kigoshi are not excluded from the composition of appealed claim 1. viii) With regards to appellant's arguments that 15 processes were used in Kigoshi, the examiner notes that, Kigoshi in several sections of the disclosure specifically mentions spray drying as a means of forming the solid dispersion (see for example, page 4, lines 38, 46, 49, 58). It is further noted that all the processes are related to each because all are used to prepare solid dispersions; and the technique of spray drying is well known in the pharmaceutical formulation art as a means of removing solvent to effect drying of compositions. ix) The polymers contemplated for use in the formation of solid dispersion of drugs in Kigoshi are all polymers that disperse the drugs. Different categories of polymers are disclosed and HPMCAS is one of 10 of the cellulose type polymers that form solid dispersion of drugs. Further also, HPMCAS is one of 4 preferred enteric coating polymers (page 4, lines 5-9) for use in forming the solid dispersions. Therefore,

Kigoshi anticipates solid dispersions and anticipates the use of spray drying as one of the drying techniques in the formation of solid dispersions.

JP 57-176907: Appellant argues that JP 57-176907 does not teach any specifics of how the spray drying was accomplished.

In response to the above, the examiner notes that the appealed claims are directed to products or composition and the prior art does not have to teach the method steps of how the product of the appealed claimed products are formed in order to anticipate the product when the appealed claims do not recite method steps and how spray drying is accomplished.

Miyajima or Kigoshi (claim 1 and claims dependent thereon): Appellant argues that the "consists of" language of the claims limits the dispersion to a two component solid dispersion of low solubility drug and HPMCAS; and that at best Miyajima teaches how to make three or four component compositions and none by spray drying; that Kigoshi discloses 22 polymers and 15 different process. Appellant cites Ex parte Davis, Ex parte Beuther and MoneyIN, Inc. V. VeriSign.

The examiner disagrees. The appealed compositions are not limited to two components of drug and HPMCAS because the comprising language of the claims is open (see line 1 of appealed claim 1). With regards to Kigoshi, all the polymers contemplated for use in the formation of solid dispersion of drugs in Kigoshi are all polymers that disperse the drugs. Different categories of polymers are disclosed and HPMCAS is one of 10 of the cellulose type polymers that form solid dispersion of drugs. Also, HPMCAS is one of 4 preferred enteric coating polymers (page 4, lines 5-9). With regards to appellant's arguments that 15 processes were used in Kigoshi, the examiner notes that, Kigoshi in several sections of the disclosure

specifically mentions spray drying as a means of forming the solid dispersion (see for example, page 4, lines 38, 46, 49, 58). It is further noted that all the processes are related to each because all are used to prepare solid dispersions.

With regards to Net MoneyIN inc. v. VeriSign Inc., the examiner notes that the issue in that case was an issue of "means plus function language" of the claims and the current claims are not drafted as "means plus function."

With regards to Ex parte Beuther, because, the polymers in Kigoshi are all related to each other in the sense that they all used to form solid dispersions of drugs, it appears the Ex parte Beuther findings support the combination since the finding by the Board in that case was that "portions of the disclosure not directly related to each other by the teachings of the reference" were used. Here, all the polymers are related.

With respect to Ex parte Davis, the examiner notes that the appealed composition in appealed claim 1 are not limited to a two component composition because the comprising language of the claim in line 1 is open and signals that the entire claim is open ended. See *in re Crish* at 73 USPQ2d 1364.

Claims 1, 23, 50 and 51 (Miyajima or Kigoshi): Appellant argues that the examiner conceded that the neither Miyajima nor Kigoshi taught particles that are less than 100 micron as required by claim 23; that the examiner also failed to clearly articulate why the claimed invention would have been obvious, in the office action of 11/9/2009.

The examiner disagrees. With regards to claim 1, the examiner has discussed how claim 1 was anticipated under 35 USC 102 and it was thus sufficient to state that claim 1 has been shown above to be anticipated by Miyajima or Kigoshi. Yes, the examiner conceded that

Miyajima and Kigoshi did not specifically say that the particles are less than 100 microns. But when a core of less that 100 microns are spray coated, then it flows that the spray coated particles must be less than 100 microns. Also, Miyajima teaches that formulation can be in the form of powder (see at least page 5, line 14) and usually the particle size of powders is in the micron size range.

With regards to claims 50 and 51, the examiner noted that since the products of Miyajima and Kigoshi are spray dried and the composition of the appealed claims are spray dried, it is reasonable to expect that the compositions of Miyajima and Kigoshi would also have residual solvent. Appellant has not provided any factual showing that it would not. Claims 50 and 51 depend from claim 1 that did not specify the volume of the solvent; also Kigoshi and Miyajima teach the claimed ratio of drug :polymer so that it is reasonable to expect that the compositions of Miyajima and Kigoshi would have residual solvent just at the appealed claim 1.

Claims 1, 4 36, 37, 49-51 and 53-56 (Kigoshi in view of Bymaster: Appellant argues that Kigoshi fails to teach the subject matter of claim 1 as pointed out above.

The examiner disagrees because it has been argued above that Kigoshi teaches the subject matter of claim 1 and that response is incorporated here.

Claims 1, 4 36, 37, 49-51 and 53-56 (Kigoshi in view of Pubmed and Bymaster):

Appellant argues that the examiners reasoning with regards to claims 4, 49, 51 and 54 deals with the examiner reading limitation into the claims and that there is nothing in claim 4 that is directed to the properties of the dosage form; that claim 49 recites solidification speed, claim 51 is not a product by process claim but a recitation of the solution from which particles are

spray dried, that the examiner failed to provide the motivation to combine Pubmed, Bymaster and Kigoshi.

In response to appellant's argument above, the examiner notes that claim 1 describes any generic drug that is sparingly soluble in water, and this same any drug is identified as being amorphous when undispersed. Thus, no limitation was read into the claims. The amorphous state of nature of the drug before dispersion is a characteristic of the drug and thus the property of the drug. The drug in Kigoshi, meeting the drug limitation of claim 1 would also be amorphous when undispersed because same products/compositions must have the same properties. Contrary to appellant's statement regarding claims 49 and 51, a solidification speed of 2 seconds of the composition of claim 1 is the characteristic property of the composition and claim 51 is a product by process claim reciting how the product of claim 1 is formed since "a recitation of the solution from which particles are spray dried" is a process limitation.

It is clearly stated in the rejection of claims 1, 4, 36, 37 49-51 and 53-56 under 35 U.S.C. 103(a) over Kigoshi in view of Madhusoodanan and further in view of Bymaster that drugs such as the antipsychotic drug, risperidone is known in the art to have effect on psychosis related to dementia, bipolar disorder and schizophrenia according to the abstract of Madhusoodanan in J. Clin. Psychiatry, 1995 Nov; and further also, that risperidone and ziprasidone are known anti-psychotic drugs according to Bymaster at column 2, lines 22 and 43. It was stated that one anti-dementia agent can be used in place of the other with the expectation that either will deliver the desired anti-dementia effect. The expectation to have the anticipated anti-dementia effect is reasonable for the substitution. Risperidone and Ziprasidone are known in the art to be sparingly soluble in water and the prior art does not have to disclose what is well known in the

art. Appellant has not shown or argued that these drugs are soluble in water. Bymaster as acknowledged by appellant is relied upon to show that Risperidone and Ziprasidone are antipsychotics and pharmaceutically equivalent. Bymaster was not relied upon for teaching a composition that comprises one or two or more antipsychotics and one or two or more serotonin reuptake inhibitors or for contemplating amorphous dispersions.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Blessing M. Fubara

/Blessing M. Fubara/
Primary Examiner, Art Unit 1618

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